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The increased recognition of proteins in critical illness

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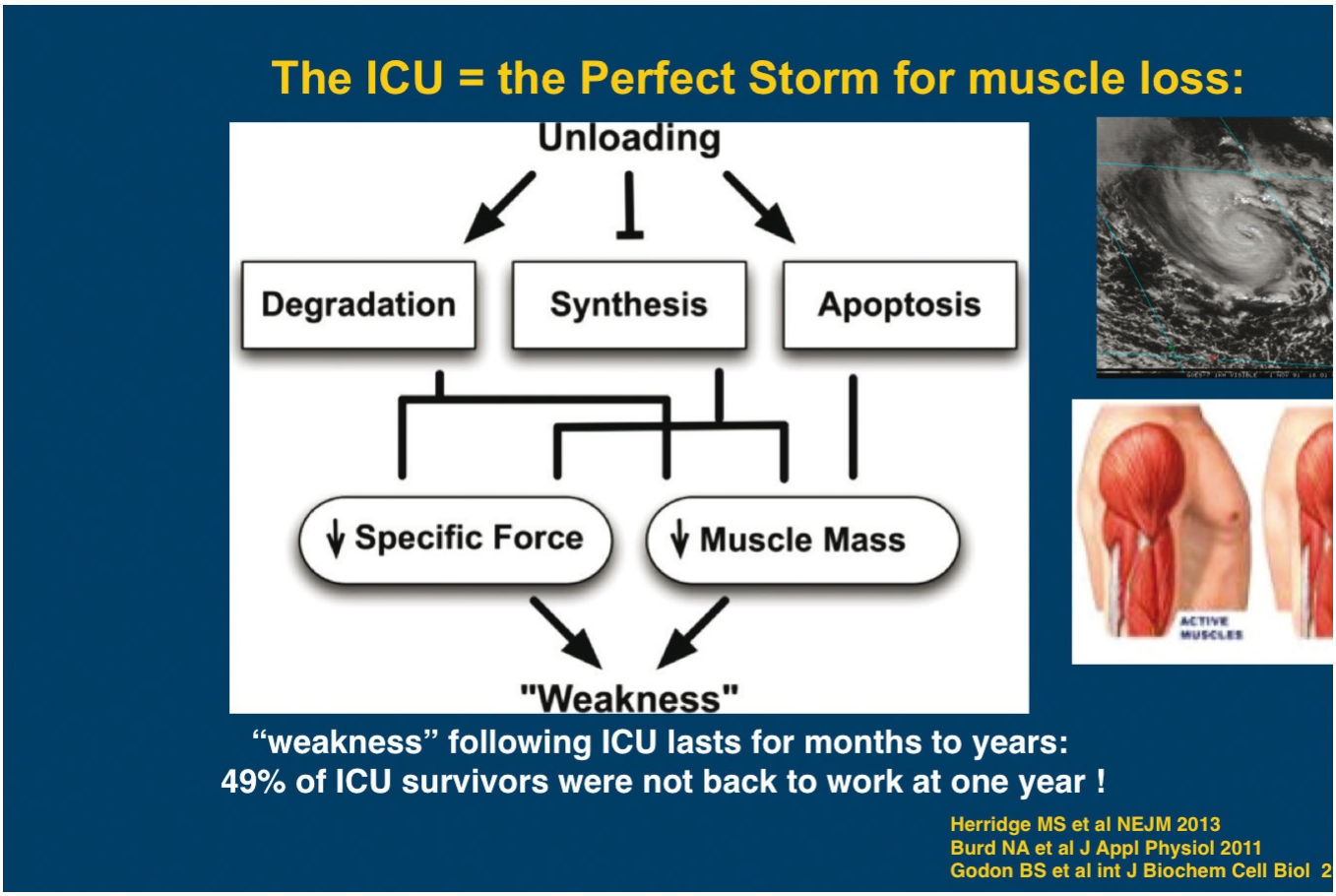
There are many new concepts and old controversies surrounding nutrition in critical care such as: the role of trophic feeding, permissive underfeeding, the use of immune modulating agents, and the optimal timing of nutrient delivery. However, enteral nutrition and protein delivery have consistently been found to be beneficial.

Traditionally, the concerns in the ICU were about meeting energy requirements while protein levels were rarely considered. Early work carried out in the 1920s by Cuthbertson had largely been forgotten until the 1980s.

Conditions in the ICU result in loss of muscle mass: patients are immobile, often have minimal energy and protein delivery, and undergo little or no resistance exercise. [30-32] Twenty-one days after a single blunt injury, 16% of total body protein is lost, 67% of it from the muscle.[33] Resting energy expenditure (REE) increases progressively over the first week to 40% above normal and can still be elevated after three weeks.



Conventional methods of analysis may not give a true picture of the rate of muscle loss. Ultrasound of the rectus femoris muscle in ICU patients showed a loss of around 10% within 10 days; but biopsies showed a thinning of muscle collagen fibres by 17.5% and when using a ratio of DNA to cellular protein, a loss of 29.5% is seen.[34] Significant inflammatory changes in skeletal muscle were observed despite patients being given an average of 0.7g/kg/day of protein.

Muscle loss is not confined to extremity skeletal muscle. A study investigating muscular volumetric changes compared the diaphragm to extremity skeletal muscle and found that there was greater loss of the diaphragm muscle. [35]

A recent study investigating mechanisms of chronic muscle wasting in elderly ICU patients found that most parameters such as proteolysis, autophagy and inflammatory cells normalised at six months, but satellite cells remained consistently depressed.[36] Satellite cells appear to regulate the ability of muscle to recover from major loss, therefore if these cells are compromised, there is a decreased ability to regenerate muscle. ICU-acquired weakness and muscle wasting has a complex aetiology but increased protein degradation, reduced protein synthesis and often limited protein intake play a part.[37]

The loss of muscle mass is dramatically increased on admission to an ICU. If inadequate protein is not supplied to these catabolic patients muscle lost during hospitalisation may never be regained. It has been reported that short term amino acid infusions improve protein balance and small randomised clinical trials with parenteral nutrition show modest benefi ts in muscle strength and fatigue.[38-41]

Questions still surround the optimal target for protein. There are numerous studies supporting protein delivery in the ICU from 0.8g/kg/day up to 2.5g/kg/ day. Large observational studies of ICU patients report most critically ill patients receive around 0.6g/kg/day of protein. Several studies consistently support that the goal for protein delivery should be at least 1.5g/kg/day and possibly higher.[41-45]

There is no consensus as yet on the upper limit. Some clinicians advocate delivery of up to 3g/kg/day (in adolescent patients), but guidelines are generally consistent in recommending an upper limit of 2.5g/kg/day. [46,47] There are

potential issues with excess protein including azotaemia, hepatic protein synthesis and altered mental status which are more theoretical than observed.[48,49]

A number of studies have demonstrated that infusion of exogenous amino acids can improve whole-body protein balance, without increasing amino acid oxidation rates in critically ill patients. [38,50,51] A higher protein intake was generally associated with an improved nitrogen balance, with dosages of 2g/kg/day being more successful than lower intakes.[52]

There is also concern that protein delivery may affect the autophagy balance. Nutrient delivery inhibits autophagy but activates cellular protein synthesis so there is not a simple direct relationship between feeding (or starvation) and autophagy.

Could anabolic resistance be a factor in ICU patients? Anabolic resistance is driven by an insensitivity to the anabolic effects of amino acids, particularly leucine. Although we do not have definitive answers for overcoming anabolic resistance we do know that certain approaches, such as hypercaloric PN or EN, hypocaloric feeding, use of anti-inflammatory, and appetite stimulants do not work.

On the other hand we know that certain interventions work consistently to protect lean body mass: protein supplementation, delivered by pulsed bolus; early enteral feeding, which protects the gut barrier and decreases systemic inflammation; metabolic modulation with nutrients such as leucine, arginine, and specialised pro-resolving molecules (SPMs); glycaemic control, resistance exercise and support for the microbiome. Other interventions appear to work in other patient groups but have not yet been confirmed as of benefit in the ICU.

In conclusion, there is good evidence to support protein in the ICU is beneficial although delivery must be individualised. An upper range of 2.5g/kg/day is considered safe. Optimal protein intake may be different in the acute compared to the prolonged phase of illness. Due to the heterogeneous nature of the ICU population decisions must be made on an individual basis. Aggressive protein delivery combined with resistance exercise may improve muscle kinetics, metabolism and regeneration. Most of our evidence currently comes from observational trials, which may not be consistent with RCTs and there are still many unanswered questions.

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